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Peptides as shuttles for drug delivery to the brain

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The breakthrough concept that proteins function as a contact network rather than as independent individuals is not only one of the most important advances in our comprehension of living systems, but also translates to a new era in drug discovery. The few reported examples of diseases caused by "impolite" protein social behavior certainly represent only the tip of the iceberg. Therapeutic intervention through molecules designed to selectively modulate the strength and specificity of protein-protein interactions (PPIs) is becoming a reality. In this context, peptides are destined to play a major role as therapeutic agents. My laboratory is contributing to speeding up this process. On the one hand, we devote efforts to studying the molecular details and dynamics of the events that occur during molecular recognition at protein surfaces. We succeeded to design and synthesize peptides able to modulate these recognition events either permanently or in response to light.[1] On the other hand, we are discovering and designing peptides able to cross biological barriers. Our aim is to use these peptides as shuttles for targeting therapeutic agents to organs, tissues, or cells, with a special emphasis on drug delivery to the brain. The treatment of CNS disorders is severely hampered by the presence of the blood-brain barrier (BBB). Several peptides have emerged as 'privileged' structures with the capacity to cross the BBB efficiently and thus as potential BBB-shuttles for drug delivery into the brain.[2] Degradation by proteases is, however, an important limitation of this approach. In recent years, we have focused on the use of non-proteinogenic amino acids, including D-amino acids, for the design of BBB-shuttles that are resistant to degradation by proteases.[3,4]
Given their capacity to reach the CNS without causing inflammation, venoms are a potentially rich source of novel BBB-shuttles. We have recently explored the use of venom-derived cyclic peptides as protease-resistant BBB-shuttles. Apamin is an 18-mer peptide from bee venom that accumulates in significant amounts in the brain and spinal cord. Starting from apamin, we have designed a series of simplified peptides stabilized via cyclization either via a disulfide bridge or through lactamization (see figure). Among these molecules, MiniAp-4 has proved to be the most permeable candidate and, accordingly to preliminary studies, it is able to promote the translocation of proteins and nanoparticles both in a human-cell-based assay and in vivo brain.[5,6]

References
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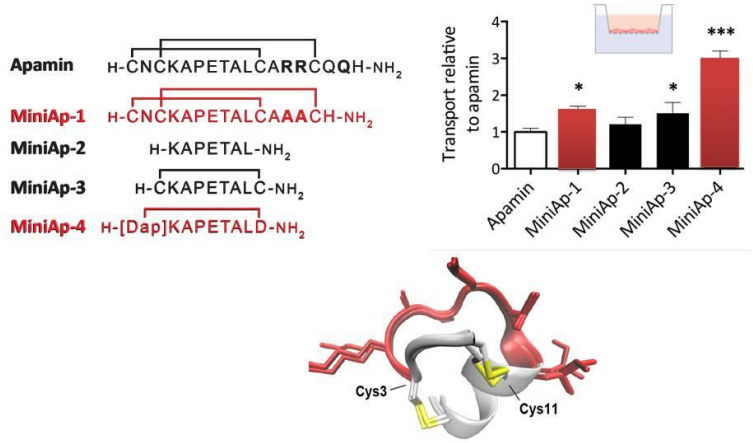

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